Response to Letter to the Editor: "Clinical but Not Histological Outcomes in Males With 45,X/46,XY Mosaicism Vary Depending on Reason for Diagnosis"

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We are thankful for the opportunity to respond to the letter by Dumeige and Martinerie commenting on our study (1) on the clinical and histological outcomes in males with 45,X/46,XY mosaicism. We appreciate their interest in our report.

First, we agree that the data presented in our report support the conclusion that most patients, regardless of genital phenotype and reason for referral, will have short stature. Nonetheless, we also found that patients for whom 45,X/46,XY mosaicism was diagnosed because of genital anomalies found at birth will be significantly shorter, both in absolute height (cm) and in age-corrected SD scores, compared with those with mosaicism diagnosed later in life, despite a trend toward a greater percentage being treated with growth hormone (41% vs 17%; $P = 0.066$; Table 1) (1). The difference between the groups was no longer statistically significant when accounting for genetic potential, a fact we also discussed in our report. Additionally, clinical outcomes, such as the rates of spontaneous pubertal onset and testosterone replacement/supplementation therapy, also differed significantly between the groups (Table 1) (1). We believe that these constitute important health outcomes and, therefore, concluded that individuals with a diagnosis of 45,X/46,XY mosaicism because of genital anomalies will have poorer health outcomes. Moreover, the clinical findings in males with 45,X/46,XY mosaicism, including growth retardation and spontaneous pubertal onset, have been corroborated by numerous other studies, including studies by Dumeige and Martinerie (2–7), and were also thoroughly discussed in our report.

We agree that both inhibin B concentrations and cytogenetic findings on gonadal tissues would have been an important addition to our study. Several of our coauthors have previously reported inhibin B and detailed cytogenetic data from patients with 45,X/46,XY mosaicism (3). However, our multicenter, retrospective design, although the greatest strength of our study, also resulted in some important limitations. Inhibin B and detailed cytogenetic data were simply not available from a sufficient number of patients to add value to the analyses.

Overall, the clinical outcomes examined in our study (*e.g.*, growth, gonadal function in terms of spontaneous puberty and reproductive hormones, need for hormone supplementation/replacement therapy) were significantly worse for the group of patients with mosaicism diagnosed at birth. However, the patients in both groups were affected by all the outcomes. This was in contrast to the histological outcomes (risk of preneoplasia and chance of spermatogenesis), which we found to be unrelated to the genital phenotype at birth. We, therefore, considered the title "Clinical but Not Histological Outcomes in Males With 45,X/46,XY Mosaicism Vary Depending on Reason for Diagnosis" to appropriately summarize the findings of our study.

Finally, and most importantly, we are in complete agreement that all patients with a 45,X/46,XY karyotype should undergo regular follow-up examinations with screening for comorbidities and gonadal neoplasia, regardless of the reason for the diagnosis. We find it appropriate to repeat a statement highlighted in the very last sentence of our report: "In general, the data indicate the importance of highly personalized medical management" (1).

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Additional Information

Disclosure Summary: The authors have nothing to disclose.

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